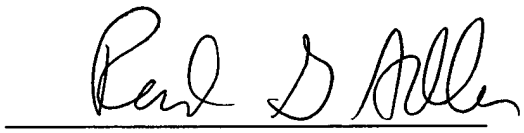
REMARKS

Applicants have amended the specification to incorporate the sequence identifiers where appropriate. Applicants submit that no new prohibited matter has been introduced by this Preliminary Amendment. Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned Version with markings to show changes made.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **Constructive Petition for Extension of Time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted,

Morgan, Lewis & Bockius LLP



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

The paragraph at page 14, line 14 through page 15, line 11 has been amended as follows:

In detail, the present invention provides six β subunit peptides possessing a tyrosine residue which can be phosphorylated by a cellular tyrosine kinase. The cytoplasmic domain sequences of each of the characterized β subunits, with the corresponding phosphorylation site identified, are:

β1 subunit: NH-D-T-G-E-N-P-I-Y(PO_3)-K-S-A-V-T-T-V-V-N-P-K-Y(PO_3)-E-G-K-COOH (SEQ ID NO. 1)

β2 subunit: NH-D-L-R-E-Y(PO_3)-R-R-F-E-K-E-K-L-S-Q-W-N-N-D-N-P-L-F-K-S-A-T-COOH (SEQ ID NO. 2)

β3 subunit: NH-D-T-A-N-N-P-L-Y(PO_3)-K-E-A-T-S-T-F-T-N-I-T-Y(PO_3)-R-G-T-COOH (SEQ ID NO. 3)

β5 subunit: NH-E-M-A-S-N-P-L-Y(PO_3)-R-K-P-I-S-T-H-T-V-D-F-T-F-N-K-F-N-K-S-Y(PO_3)-N-G-T-V-D-COOH (SEQ ID NO. 4)

β6 subunit: NH-Q-T-G-T-N-P-L-Y(PO_3)-R-G-S-T-S-T-F-K-N-V-T-Y(PO_3)-K-H-R-E-K-Q-K-V-D-L-S-T-D-C-COOH (SEQ ID NO. 5) or

NH-Q-T-G-T-N-P-L-Y(PO_3)-R-G-S-T-S-T-F-K-N-V-T-Y(PO3)-K-H-R-COOH (SEQ ID NO. 6)

β7 subunit: NH-D-R-R-E-Y-(PO_3)-S-R-F-E-K-E-Q-Q-Q-L-N-W-K-Q-D-S-N-P-L-Y(PO_3)-K-S-A-I-COOH (SEQ ID NO. 7).

The paragraph beginning at page 19, line 18, has been amended as follows:

Any integrin which contains a phosphorylated tyrosine in the cytoplasmic domain of the β subunit can be used for identifying and isolating an integrin cytoplasmic signaling partner. These particularly include the β1, β2, β3, β5, β6, β7 and β8 subunits, but other β subunits are contemplated. These particularly exclude β subunits in which the phosphorylated tyrosine is followed by an isoleucine or leucine in an ITAM motif (YXXI/L) (SEQ ID NO. 8).

The paragraph beginning at page 42, line 15 through page 43, line 6, has been amended as follows:

In light of our discovery, the following observations are relevant. The NPLY sequence encompassing residues 744-747 of GPIIIa is homologous to the NPXY motif which, when phosphorylated on tyrosine, is known to bind proteins with the phosphotyrosine-binding (PTB) domain such as SHC, IRS-1, and possibly pp140 kDa (Kavanaugh, W.M. *et al.*, *Science* (1994) 266:1862-1865; Gustafson, T.A. *et al.*, *Mol. Cell Biol.* (1995) 15:2500-2508). There also exists an immune receptor tyrosine-based activation motif (ITAM; YXXL/IXXXXXXXXYXXL/I) (SEQ ID NO. 9) found on subunits of the T cell receptor, B cell receptor, and Fc receptor which are, when phosphorylated on both tyrosines, known to interact with signaling proteins (e.g., ZAP-70 in T cells or syk in B cells) (Chan, A.C. *et al.*, *Cell* (1992) 71:649-662; Hutchcroft, J.E. *et al.*, *J. Biol. Chem.* (1992) 267:8613-8619; Law, D.A. *et al.*, *Curr. Biol.* (1993) 3:645-657. It is noted that the sequence in the β3 subunit, although containing two tyrosine residues, lacks the L/I residues found in all ITAM domains. Therefore, the β3 cytoplasmic domain does not appear to contain an ITAM motif. However, the cytoplasmic domain of the β4 integrin, which does not bear homology to the other integrin β subunits, does contain an ITAM domain. Like other ITAMs, this domain has recently been shown to act in the recruitment of signaling molecules (Mainiero, F. *et al.*, *EMBO J.* (1995) 14:4470-4481). Accordingly, experimental protocols were developed to determine whether the tyrosine residues within the GPIIIa were also phosphorylated in response to stimuli which activate the GPIIb-IIIa integrin.

The paragraph beginning at page 47, line 14, has been amended as follows:

The discovery that the cytoplasmic domain of GPIIIa is phosphorylated at tyrosine residues during platelet aggregation was the first step in demonstrating that the phosphorylated cytoplasmic domain has functional activity in interacting with signaling proteins. A phosphorylated peptide corresponding residues 740-762 of GPIIIa was synthesized and coupled to biotin at the main terminus:

(Peptide 1) Biotin-D-T-A-N-N-P-L-Y(PO_3)-K-E-A-T-S-T-F-T-N-I-T-Y(PO_3)-R-G-T-COOH (SEQ ID NO. 3)

The paragraph beginning at page 47, line 23, has been amended as follows:

A control peptide was synthesized with an identical sequence, but unphosphorylated:

(Peptide 2) Biotin-D-T-A-N-N-P-L-Y-K-E-A-T-S-T-F-T-N-I-T-Y-R-G-T-COOH (SEQ ID NO. 10).

The paragraph beginning at page 52, line 3, has been amended as follows:

The following peptides are used to demonstrate the binding of signaling partners to integrins containing a phosphorylated β1 subunit:

(peptide 1) biotin-D-T-G-E-N-P-I-Y(PO_3)-K-S-A-V-T-T-V-V-N-P-K-Y(PO_3)-E-G-K-COOH (SEQ ID NO. 1)

and the unphosphorylated control peptide

(peptide 2): biotin-D-T-G-E-N-P-I-Y-K-S-A-V-T-T-V-V-N-P-K-Y-E-G-K-COOH (SEQ ID NO. 11).

The paragraph beginning at page 54, line 23 through page 55, line 7, has been amended as follows:

The following peptides are used to demonstrate the binding of signaling partners to integrins containing a phosphorylated β5 subunit:

(peptide 1) biotin-E-M-A-S-N-P-L-Y(PO_3)-R-K-P-I-S-T-H-T-V-D-F-T-F-N-K-F-N-K-S-Y(PO_3)-N-G-T-V-D-COOH (SEQ ID NO. 4)

[A]and the unphosphorylated control peptide:

(peptide 2) biotin-E-M-A-S-N-P-L-Y-R-K-P-I-S-T-H-T-V-D-F-T-F-N-K-F-N-K-S-Y-N-G-T-V-D-COOH (SEQ ID NO. 12).

The paragraph beginning at page 57, line 8, has been amended as follows:

The following peptides are used to demonstrate the binding of signaling partners to integrins containing a phosphorylated β6 subunit:

(peptide 1): biotin-Q-T-G-T-N-P-L-Y(PO_3)-R-G-S-T-S-T-F-K-N-V-T-Y(PO_3)-K-H-R-E-K-Q-K-V-D-L-S-T-D-C-COOH (SEQ ID NO. 5)

and t[T]he unphosphorylated control peptide:

(peptide 2): biotin-Q-T-G-T-N-P-L-Y-R-G-S-T-S-T-F-K-N-V-T-Y-K-H-R-E-K-Q-K-V-D-L-S-T-D-C-COOH (SEQ ID NO. 13).

The paragraph beginning at page 57, line 19, has been amended as follows:

Alternatively, a phosphorylated peptide missing the 11 carboxy terminal amino acids, which may have an influence on signaling through this integrin, can be used. This peptide is used to identify signaling proteins which do not recognize the entire cytoplasmic domain.

(peptide 3): biotin-Q-T-G-T-N-P-L-Y(PO_3)-R-G-S-T-S-T-F-K-N-V-T-Y(PO_3)-K-H-R-COOH (SEQ ID NO. 6).

The paragraph beginning at page 60, line 14, has been amended as follows:

The following peptides are used to demonstrate the binding of signaling partners to integrins containing a phosphorylated β2 subunit:

(peptide 1): biotin-D-L-R-E-Y(PO_3)-R-R-F-E-K-E-K-L-S-Q-W-N-N-D-N-P-L-F-K-S-A-T-COOH (SEQ ID NO. 2)

[A]and the unphosphorylated control peptide:

biotin-D-L-R-E-Y-R-R-F-E-K-E-K-L-S-Q-W-N-N-D-N-P-L-F-K-S-A-T-COOH (SEQ ID NO. 14)

The paragraph beginning at page 62, line 9, has been amended as follows:

The following peptides are used to identify signaling proteins associated with the β7 cytoplasmic tail in a phospho-dependent manner. These peptides are used to precipitate proteins from suitable cell lysates (e.g., differentiated THP-1 cells as described above), and for cDNA library screening.

biotin-D-R-R-E-Y(PO_3)-S-R-F-E-K-E-Q-Q-Q-L-N-W-K-Q-D-S-N-P-L-Y(PO_3)-K-S-A-I-COOH (SEQ ID NO. 7)

[A]and the unphosphorylated control peptide:

biotin-D-R-R-E-Y-S-R-F-E-K-E-Q-Q-Q-L-N-W-K-Q-D-S-N-P-L-Y-K-S-A-I-COOH (SEQ ID NO. 15).